Attachment C

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(56) Documents cited
EP 0490587 A1 EP 0400974 A2 EP 0400835 A1

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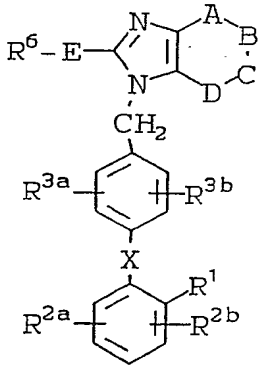
INT CL[5] A61K 31/415
Online database: CAS-ONLINE

(54) Substituted imidazo-fused 6-membered carbocycle or heterocycle as neurotensin antagonists

(57) Treating disease states mediated by neurotensin by administering to a patient in need of treatment a therapeutically effective amount of a neurotensin antagonist which is useful against GI and CNS disorders which is a substituted imidazo-fused 6-membered carbocycle or heterocycle of structural formula I as disclosed in EP-0400974-A2 and EP-0400835-A2:



(I)

wherein A, B, C, and D are independently carbon atoms or nitrogen atoms.

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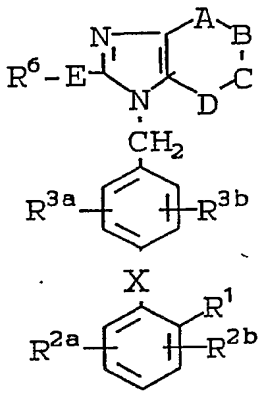
SUBSTITUTED IMIDAZO-FUSED 6-MEMBERED CARBOCYCLE OR HETEROCYCLE AS NEUROTENSIN ANTAGONISTS

INTRODUCTION OF THE INVENTION

This invention is concerned with a method of treating disease states mediated by neurotensin by the administration to a patient in need of treatment of a therapeutically effective amount of a neurotensin antagonist which is a substituted imidazo-fused 6-membered carbocycle or heterocycle of structural formula I:



(I)

wherein A, B, C, and D are independently carbon atoms or nitrogen atoms.

As neurotensin antagonists these compounds find utility in the treatment of CNS dysfunctions such as psychoses, depression, cognitive dysfunction, such as Alzheimer's disease, anxiety, tardive dyskinesia, drug dependency, panic attack and mania. The neurotensin antagonist property also imparts to the compounds utility in GI disorders such as gastroesophageal reflux disorder (GERD), irritable bowel syndrome, diarrhea, cholic, ulcer, GI tumors, dyspepsia, pancreatitis, esophagitis and gastroparesis. The known ability of neurotensin to release mast cell histamine indicates that antagonists will be useful in the treatment of allergic and inflammatory conditions.

BACKGROUND OF THE INVENTION

Neurotensin (NT) is a tridecapeptide hormone (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH), originally isolated from the bovine hypothalamus [Carraway, R. and Leeman, S. E., J. Biol. Chem.,248, 6854 (1973)], has subsequently been shown to be distributed in the brain [Uhl, G. R., et al., Proc. Natl. Acad. Sci. USA, 74, 4059-4063 (1977), gastrointestinal tract [1). Kitabgi, P., Carraway, R. and Leeman, S. E., J. Biol. Chem., 251, 7053 (1976); 2). Carraway, R., Kitabgi, P., and Leeman, S. E., J. Biol. Chem., 253, 7996 (1978); 3).Helmstadler, V., Taugner, C., Feurle, G. E. and Frossman, W. G., Histochemistry, 53, 35-41 (1977)] and pancreas [Feurle, G. E. and Niestroj, S., Pancreas, 6, 202-207 (1991) and references cited therein] of various animals including human [Mai, J.

K., et al., Neuroscience, 22, 499-524 (1987)]. Although the physiological role of neurotensin has not yet been clearly understood, this endogenous peptide participates in a wide spectrum of central [1). Prange, A. J. and Nemeroff, C. B., Annal. NY Acad. Sciences, 400, 368-375 (1982); 2). Stowe, Z. N.and Nemeroff, C. B., Life Sci., 49, 987-1002, (1991); 3) Kitabgi, P., Neurochem. Int., 14, 111-119 (1989); 4). Levant and Nemeroff, C. B., Current topics in Neuroendocrinology, 8, 231-262 (1988)] and peripheral [Leeman, S. E., Aronin, N. and Ferris, C., Hormone Res., 38, 93-132 (1982)] biological functions.

Neurotensin is also known to release mast cell histamine, indicating that antagonists will be useful in the treatment of allergic and inflammatory conditions, as well. [See, Rossei, S.S. and Miller, R.J., Life Sci., 31, 509-516 (1982) and Kurose, M. and Saeki, K., Eur. J. Pharmacol., 76, 129-136 (1981).]

Neurotensin, like most other peptides, is unable to cross the blood-brain barrier (BBB). However, certain peripheral effects of neurotensin have been observed after central administration of the peptide [Prange, A. J. and Nemeroff, C. B., Annal. NY Acad. Sciences, 400, 368-391 (1982). The direct application of neurotensin into the brain causes hypothermia, potentiation of barbiturate induced sedation, catalepsy, antinociception, blockade of psychostimulant-induced locomotor activity and reduced food consumption. In the central nervous system (CNS), neurotensin behaves as a

neurotransmitter or neuromodulator [1) Uhl, G. R. and Snyder, S. H., Eur. J. Pharmacol., 41, 89-91 (1977); 2) Uhl, G. R., Annal. NY Acad. Sciences, 400, 132-149 (1982)], and has been shown to have close anatomical and biochemical associations with the dopaminergic (DA) system [Nemeroff, C. B., et al. Annal. NY Acad. Sciences, 400, 330-344 (1982)]. Neurotensin increases the synthesis and the turnover of DA in rat brain. Acute and chronic treatment with clinically efficacious antipsychotic drugs (e.g., haloperidol, chloropromazine) have consistently demonstrated an increase in neurotensin concentrations in the nucleus accumbens and striatum while phenothiazines that are not antipsychotics did not produce this increase. Behaviorally, neurotensin, after central administration, mimics the effects of systemically administered neuroleptics. However, unlike classical neuroleptics (which primarily acts on D_2 receptors), neurotensin fails to bind to dopamine receptors or inhibit cAMP accumulation following DA receptor activation. Neurotensin does not block the stereotypy induced by DA agonists. The post-mortem studies of patients with schizophrenia showed an increase in the level of neurotensin in the Brodman's area 32 of human brain [Nemeroff, C. B., et. al., Science., 221, 972-975 (1983) and references cited therein], which suggest possible roles of neurotensin in the pathophysiology of this disease. Neurotensin receptors have also been implicated in Parkinson's disease and progressive supranuclear palsy [Chinaglia, G. et al., Neuroscience, 39, 351-360 (1990)].

Of the total body neurotensin in many mammalian species, more than 80% is present in the gastrointestinal tract, especially in the distal small intestine in the endocrine like N-cells. In the gut, neurotensin stimulates pancreatic secretion [Sakamoto, T.,et al, Surgery, 96, 146-53 (1984)], inhibits gastric acid secretion and gastric emptying [Blackburn, A. M., Lancet, 1, 987-989 (1980)]. Neurotensin also stimulates the growth of small intestinal mucosa in an isolated defunctional loop of jejunum, which suggests a direct systemic effect of neurotensin in the gut. In addition, neurotensin can stimulate pancreatic exocrine secretion in mammals [Iwatsuki, K., et al., Clin. Expt. Pharmacol. Physiol., 18, 475-481 (1991) and references cited therein].

From the structural work, it is evident that the biological activity of neurotensin resides within the carboxy terminal five or six amino acid residues. The C-terminal hexapeptide NT^{8-13} has displayed full biological activity of the tridecapeptide. In contrast, all amino terminal partial sequences are essentially inactive [Leeman, S. E. and Carraway, R. E., Annal. NY Acad. Sciences, 400, 1-16 (1982)]. The C-terminal COOH group and two Arg residues are essential for the biological activity of NT^{8-13} as well as neurotensin. L-amino acids are required at positions-9,10,11 and 13, and only Arg^8 can be replaced by D-Arg without loss of any activity. At the position-11, an aromatic amino acid is essential. Similarly, alkyl side-chains of Ile^{12} and Leu^{13} are also necessary for full biological activity [Kitabgi,

P., Annal. NY Acad. Sciences, **400**, 37-53 (1982)]. Most of the analogues of neurotensin examined generally behaved as agonists. However, two analogues D-Trp^{11}-NT and Tyr(Me)^{11}-NT have displayed partial antagonist activity [Rioux, F. R.,et al., Eur. J. Pharmacol., **66**, 373-379 (1980)].

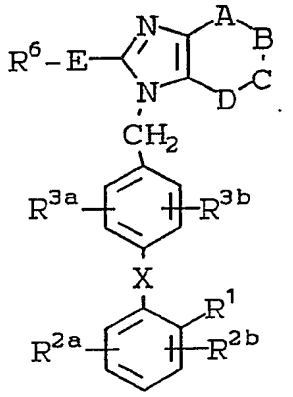
The compounds useful in the novel method of treatment of this invention are known in the art having been published in European Patent Application EP 400,835 and EP 400,974 (Merck & Co., Inc.) where they are alleged to be angiotensin II receptor antagonists useful in the treatment of hypertension and ocular hypertension. EP 400,835 disclosing benzimidazoles published on December 5, 1990, and EP 400,974 imidazo-6-fused heterocycles published on December 5, 1990.

Although there are reports of peptidic neurotensin antagonists, they are rapidly degraded in vivo and not orally active and none are useful clinically. There are no reports of non-peptidic neurotensin antagonists.

Now with this invention there are provided non-peptidic neurotensin antagonists.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the novel method of treatment of this invention have structural formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:

(a) $-NHSO_2R^{23}$,
(b) $-NHSO_2NHCOR^{23}$,
(c) $-NHCONHSO_2R^{23}$,
(d) $-SO_2NHR^{23}$,
(e) $-SO_2NHCOR^{23}$,
(f) $-SO_2NHCONR^9R^{23}$,
(g) $-SO_2NHCOOR^{23}$,
(h) $-SO_2NHOR^{23}$,
(i) $-CH_2SO_2NHCOR^{23}$,
(j) $-CH_2SO_2NHCONHR^{23}$,
(k) $-CO_2H$, or
(l) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are independently H, Cl, Br, I, F, $-NO_2$, $-NH_2$, C_1-C_4-alkylamino, di(C_1-C_4 alkyl)amino, $-SO_2NHR^9$, CF_3, C_1-C_4-alkyl, or C_1-C_4-alkoxy;

R^{3a} is

(a) H,
(b) Cl, Br, I, F,
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy,
(e) C_1-C_6-alkoxyalkyl;

R^{3b} is

(a) H,
(b) Cl, Br, I, F,
(c) NO_2,
(d) C_1-C_6-alkyl,
(e) C_1-C_6-acyloxy,
(f) C_1-C_6-cycloalkyl
(g) C_1-C_6-alkoxy,
(h) $-NHSO_2R^4$,
(i) hydroxy C_1-C_4-alkyl,
(j) aryl C_1-C_4-alkyl,
(k) C_1-C_4-alkylthio,
(l) C_1-C_4-alkyl sulfinyl,
(m) C_1-C_4-alkyl sulfonyl,
(n) NH_2,
(o) C_1-C_4-alkylamino,
(p) C_1-C_4-dialkylamino,
(q) fluoro C_1-C_4-alkyl,
(r) $-SO_2-NHR^9$,

(s) aryl, or wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of Cl, Br, I, F, C_1-C_4-alkyl, C_1-C_4-alkoxy, NO_2, CF_3, C_1-C_4-alkylthio, OH, NH_2, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl$)_2$, CO_2H, and CO_2-C_1-C_4-alkyl;

(t) furyl;

R^4 is H, C_1-C_6 alkyl, aryl or $-CH_2$-aryl;

R^{4a} is C_1-C_6-alkyl, aryl or $-CH_2$-aryl;

R^5 is H, $-\underset{\displaystyle R^4}{\underset{|}{CH}}-O-\overset{\displaystyle O}{\overset{\|}{C}}-R^{4a}$;

E is a single bond, $-NR^{13}(CH_2)_s-$, $-S(O)_x-(CH_2)_s-$ where x is 0 to 2 and s is 0 to 5, -CH(OH)-, -O-, -CO-;

R^6 is

(a) aryl unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Cl, Br, I, F, $-O-C_1$-C_4-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1$-C_4-alkyl, -OH, $-NH_2$, C_3-C_7-cycloalkyl, C_3-C_{10}-alkenyl;

(b) C_1-C_9-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which can be unsubstituted or substituted with a substituent selected from the group consisting of aryl, C_3-C_7-cycloalkyl, Cl, Br, I, F, -OH, $-NH_2$,

$-NH(C_1-C_4-alkyl)$, $-CF_2CF_3$, $-N(C_1-C_4-alkyl)_2$, $-NH-SO_2R^4$, $-COOR^4$, $-CF_3$, $-CF_2CH_3$, $-SO_2NHR^9$; or

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered cyclic ring which can contain one or two members selected from the group consisting of N, O, S, and wherein the substituents are members selected from the group consisting of -OH, -SH, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, Cl, Br, I, F, or NO_2,

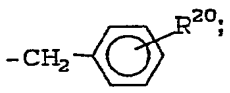
(d) perfluoro-C_1-C_4-alkyl,

(e) C_3-C_7-cycloalkyl optionally mono- or disubstituted with C_1-C_4-alkyl or $-CF_3$;

R^9 is H, C_1-C_5-alkyl, aryl or $-CH_2$-aryl;

R^{10} is H, C_1-C_4-alkyl;

R^{11} is H, C_1-C_6-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, or



R^{12} is -CN, $-NO_2$ or $-CO_2R^4$;

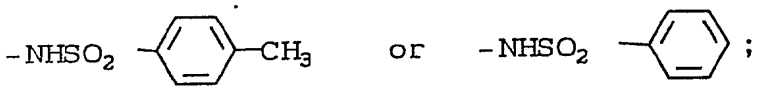
R^{13} is H, $-CO(C_1-C_4-alkyl)$, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{15} is H, C_1-C_6-alkyl;

R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,



;

R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;

R^{20} is H, $-NO_2$, $-NH_2$, $-OH$ or $-OCH_3$;

R^{22} is

(a) phenyl, unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of: Cl, Br, I, or F, $-O-C_1-C_4$-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1-C_4$-alkyl, $-OH$, $-NH_2$, $-COOR^4$, C_3-C_7-cycloalkyl, and C_3-C_{10}-alkenyl;

(b) C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, C_3-C_7-cycloalkyl, Cl, Br, I, F, $-OH$, $-O-C_1-C_4$-alkyl, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$, $-NH-SO_2R^4$, $-COOR^4$, $-SO_2NHR^9$, and $-S-C_1-C_4$-alkyl;

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered ring comprising one or two heteroatoms selected from the group consisting of N, O, and S, and wherein the substituents are members selected from the group consisting of: -OH, -SH, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, $-COOR^4$, Cl, Br, I, F, and NO_2; or

(d) C_3-C_7-cycloalkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: C_1-C_4-alkyl, -O-C_1-C_4-alkyl, -S-C_1-C_4-alkyl, -OH, $-COOR^4$, C_1-C_4-perfluoroalkyl, Cl, Br, F, and I, or

(e) (C_1-C_4)-perfluoroalkyl;

R^{23} is

(a) aryl,

(b) heteroaryl wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five- or six-membered aromatic ring which can optionally contain 1 to 3 heteroatoms selected from the group consisting of O, N or S and wherein the substituents are members selected from the group consisting of -OH, -SH, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkoxy, halo(Cl, Br, F, I), $-NO_2$, $-CO_2H$, $-CO_2$-C_1-C_4-alkyl, $-NH_2$, -NH(C_1-C_4-alkyl) and -N(C_1-C_4-alkyl)$_2$;

(c) C_3-C_4-cycloalkyl,

(d) C_1-C_8-alkyl which can be unsubstituted or substituted with one or two substituents selected from the group consisting of: aryl heteroaryl, -OH, -SH, -C_1-C_4-alkyl, -O(C_1-C_4-alkyl), -S(C_1-C_4-alkyl), -C_3-C_8-cycloalkyl, $-CF_3$, Cl, Br, F, I, $-NO_2$, $-CO_2H$, $-CO_2$-C_1-C_4-alkyl, $-CONR^4R^{22}$, $-OCONR^4R^{22}$, $-NH_2$, -NH(C_1-C_4-alkyl), $-NHCOR^{4a}$, NR^4COOR^9 -N(C_1-C_4-alkyl)$_2$, $-NR^4COR^{22}$, $-NR^4SO_2R^{22}$, $-SO_2NR^4R^{22}$, $-PO_3H$, -PO(OH)(C_1-C_4-alkyl), -PO(OH)(aryl), or -PO(OH)(O-C_1-C_4-alkyl),

(e) perfluoro-C_1-C_4-alkyl;

X is absent or is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,

(e) $-\underset{\underset{R^{13}}{|}}{N}-$,

(f) $-CO\underset{\underset{R^{15}}{|}}{N}-$,

(g) $-NCO-$ (with R^{15}),

(h) $-OCH_2-$,

(i) $-CH_2O-$

(j) $-SCH_2-$,

(k) $-CH_2S-$,

(l) $-NHC(R^9)(R^{10})$,

(m) $-NR^9SO_2-$,

(n) $-SO_2NR^9-$,

(o) $-C(R^9)(R^{10})NH-$,

(p) $-CH=CH-$,

(q) $-CF=CF-$,

(r) $-CH=CF-$,

(s) $-CF=CH-$,

(t) $-CH_2CH_2-$,

(u) $-CF_2CF_2-$,

(v) $-CH-CH-$ and $C\begin{matrix}CH_2\\ \\ CH_2\end{matrix}$,

Z is O, NR^{13} or S;

-A-B-C-D- represents the constituent atoms of a 6-member carbocycle or a 6-member saturated or unsaturated heterocyclic ring with the imidazole to which they are attached containing 1 to 3 nitrogen atoms and includes the following:

(a) $-\overset{R^7}{\underset{|}{C}}=\overset{R^7}{\underset{|}{C}}-\overset{R^7}{\underset{|}{C}}=\overset{R^7}{\underset{|}{C}}-$,

(b) $-\overset{R^7}{\underset{|}{C}}=\overset{R^7}{\underset{|}{C}}-\overset{R^7}{\underset{|}{C}}=N-$,

(c) $-N=\overset{R^7}{\underset{|}{C}}-\overset{R^7}{\underset{|}{C}}=\overset{R^7}{\underset{|}{C}}-$,

(d) $-\overset{R^7}{\underset{|}{C}}=\overset{R^7}{\underset{|}{C}}-N=\overset{R^7}{\underset{|}{C}}-$,

(e) $-\overset{R^7}{\underset{|}{C}}=N-\overset{R^7}{\underset{|}{C}}=\overset{R^7}{\underset{|}{C}}-$,

(f) $-\overset{R^7}{\underset{|}{C}}=\overset{R^7}{\underset{|}{C}}-N=N-$,

(g) $-N = N - \overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}}-$,

(h) $-\overset{R^7}{\underset{|}{C}} = N - N = \overset{R^7}{\underset{|}{C}} -$,

(i) $-N = \overset{R^7}{\underset{|}{C}} - \overset{R^7}{\underset{|}{C}} = N-$,

(j) $-N = \overset{R^7}{\underset{|}{C}} - N = \overset{R^7}{\underset{|}{C}}-$,

(k) $-\overset{R^7}{\underset{|}{C}} = N - \overset{R^7}{\underset{|}{C}}= N-$,

(l) $-N = N - N = \overset{R^7}{\underset{|}{C}}-$,

(m) $-\overset{R^7}{\underset{|}{C}} = N - N = N-$,

(n) $-N = N - \overset{R^7}{\underset{|}{C}} = N-$,

(o) $-N = \overset{R^7}{\underset{|}{C}} - N = N-$,

(p) $-\overset{O}{\overset{\|}{C}} - \overset{R^8}{\underset{|}{N}} - \overset{O}{\overset{\|}{C}} - \overset{R^8}{\underset{|}{N}}-$,

(q) $-\overset{R^8}{\underset{/}{N}} - \overset{O}{\overset{//}{C}} - \overset{R^8}{\underset{/}{N}} - \overset{O}{\overset{//}{C}}-$,

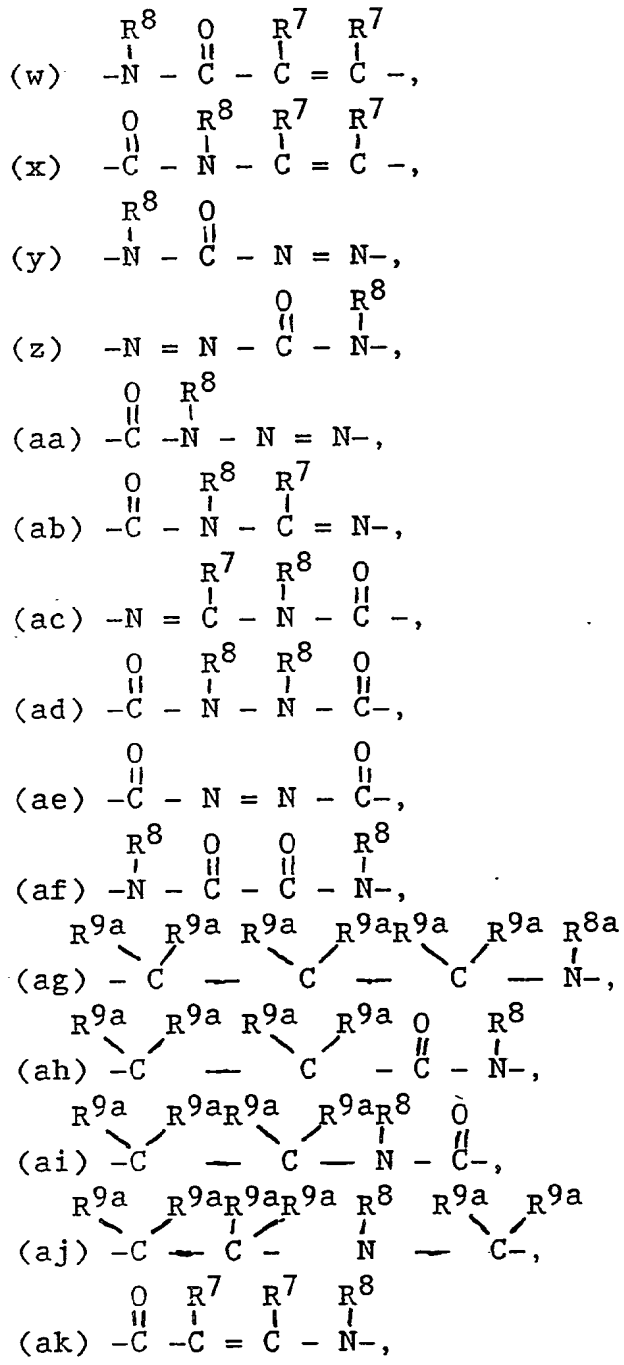
(r) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{O}{\overset{\|}{C}} - \overset{R^8}{\underset{|}{N}} -$,

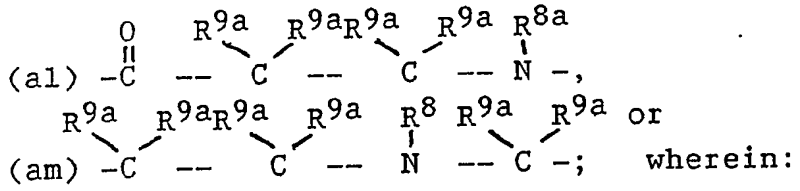
(s) $-\overset{R^8}{\underset{|}{N}} - \overset{O}{\overset{\|}{C}} - \overset{R^7}{\underset{|}{C}} = N-$,

(t) $-N = \overset{R^7}{\underset{|}{C}} - \overset{O}{\overset{\|}{C}} - \overset{R^8}{\underset{|}{N}} -$,

(u) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{O}{\overset{\|}{C}} - \overset{R^8}{\underset{|}{N}}-$,

(v) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{R^8}{\underset{|}{N}} - \overset{O}{\overset{\|}{C}} -$,





(al) $-C(=O)-C(R^{9a})_2-C(R^{9a})_2-C(R^{9a})_2-N(R^{8a})-$,

(am) $-C(R^{9a})_2-C(R^{9a})_2-C(R^{9a})_2-N(R^{8})-C(R^{9a})_2-$; wherein:

R^7 groups can be the same or different and represent:

a) hydrogen,

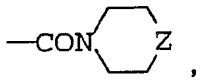
b) C_1-C_6 straight or branched chain alkyl, or C_2-C_6 alkenyl, or alkynyl each of which is unsubstituted or substituted with:

i) -OH

ii) C_1-C_4-alkoxy,

iii) $-CO_2R^4$,

iv) $-OCOR^4$,

v) 

vi) $-CON(R^4)_2$

vii) $-N(R^4)-CR^4$

viii) $-N(R^4)_2$,

ix) aryl as defined above,

x) heterocyclic as defined in (p) below,

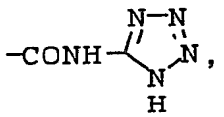
xi) $-S(O)_xR^{23}$,

xii) tetrazol-5-yl,

xiii) $-CONHSO_2R^{23}$,

xiv) $-SO_2NH$-heteroaryl,

xv) $-SO_2NHCOR^{23}$,

xvi) 

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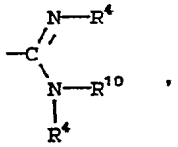

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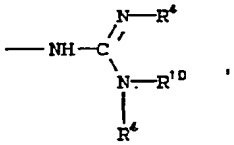


xix) $-PO(OR^4)_2$,

xx) $-PO(OR^4)R^9$,

c) Cl, Br, I, F,

d) perfluoro-C_1-C_4-alkyl,

e) $-OH$,

f) $-NH_2$,

g) $-N(R^4)-R^{23}$,

h) $-N(R^4)-COR^{23}$,

i) $-OR^{23}$,

j) $-CO_2R^4$,

k) $-CON(R^4)_2$,

l) $-NH-C_3$-C_7-cycloalkyl,

m) C_3-C_7-cycloalkyl,

n) aryl as defined above, or

o) heterocyclic which is a five- or six-membered saturated or unsaturated ring containing up to three heteroatoms selected

from the group consisting of O, N or S wherein S may in the form of sulfoxide or sulfone and which may be optionally substituted with one or two substituents which are members selected from the group consisting of Cl, Br, F, I, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-$S(O)_x$- where x is as defined above, CF_3, NO_2, OH, CO_2H, CO_2-C_1-C_4-alkyl, or $-N(R^4)_2$;

p) -CN,

q) $(CH_2)_nN$- wherein n is 4 to 6,

r) $-SO_2N(R^4)_2$;

s) tetrazol-5-yl,

t) $-CONHSO_2R^{23}$,

u) $-PO(OR^4)_2$,

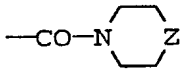
v) $-NHSO_2CF_3$,

w) $-SO_2NH$-heteroaryl,

x) $-SO_2NHCOR^{23}$,

y) $-S(O)_x-R^{23}$,

z)



,

aa) $-PO(OR^4)R^9$,

bb) $-NHSO_2R^{23}$,

cc) $-NHSO_2NHR^{23}$,

dd) $-NHSO_2NHCOR^{23}$,

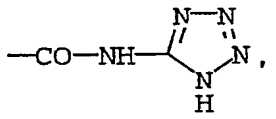
ee) $-NHCONHSO_2R^{23}$,

ff) $-N(R^4)CO_2R^{23}$,

gg) $-N(R^4)-CON(R^4)-R^{23}$,

hh) $-CO-aryl$,

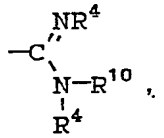
ii)



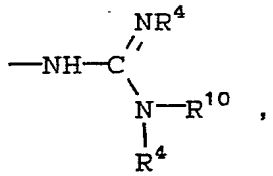
jj) $-CO-C_1-C_4-alkyl$,

kk) $-SO_2NH-CN$,

ll)



mm)



R^8 groups can be the same or different and represent:

a) hydrogen,

b) C_1-C_6-alkyl or alkenyl either unsubstituted or substituted with hydroxy, C_1-C_4-alkoxy, $-N(R^4)_2$, $-CO_2R^4$, or C_3-C_5-cycloalkyl;

c) C_3-C_5-cycloalkyl,

R^{8a} is R^8 or C_1-C_4-acyl; and

R^{9a} groups can be the same or different and represent:

a) hydrogen,

b) C_1-C_6-alkyl either unsubstituted or substituted with

i) hydroxy,

ii) $-CO_2R^4$,

iii) $-CONHR^4$, or

iv) $-CON(R^4)_2$.

The terms "alkyl", "alkenyl", "alkynyl: and the like include both the straight chain and branched chain species of these generic terms wherein the number of carbon atoms in the species permit. Unless otherwise noted, the specific names for these generic terms shall mean the straight chain species. For example, the term "butyl" shall mean the normal butyl substituent, n-butyl.

One embodiment of the novel compounds of this invention is the class compounds of Formula I wherein:

R^1 is:

(a) $-NHSO_2R^{23}$,

(b) $-NHSO_2NHCOR^{23}$,

(c) $-NHCONHSO_2R^{23}$,

(d) $-SO_2NHR^{23}$,

(e) $-SO_2NHCOR^{23}$,

(f) $-SO_2NHCONR^9R^{23}$,

(g) $-SO_2NHCOOR^{23}$,

(h) $-SO_2NHOR^{23}$,
(i) $-CH_2SO_2NHCOR^{23}$,
(j) $-CH_2SO_2NHCONHR^{23}$, or
(k) -1H-tetrazol-5-yl;

X is a single bond;

R^{2a} and R^{2b} are independently:
a) C_1-C_4-alkyl,
b) Cl, Br, I, F,
c) hydrogen;

R^{3a} and R^{3b} are independently:
a) C_1-C_6-alkyl,
b) Cl, Br, I, F, or
c) C_1-C_6-alkoxy,
d) hydrogen;

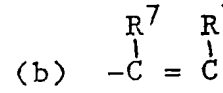
R^4 is H, or C_1-C_4-alkyl;

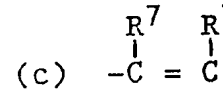
E is a single bond or -S-;

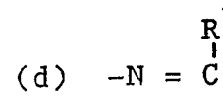
R^6 is a branched or straight chain C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl or C_2-C_6- alkynyl each of which is either unsubstituted or substituted with C_1-C_4-alkylthio, C_1-C_4-alkoxy, CF_3, CF_2CF_3 or $-CF_2CH_3$;

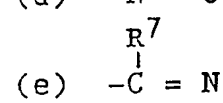
A-B-C-D- represents:

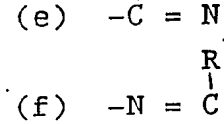
(a) $-\overset{R^7}{C} = \overset{R^7}{C} - \overset{R^7}{C} = \overset{R^7}{C}-$,

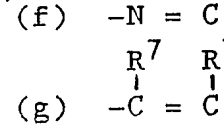
(b) 

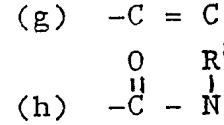
(c) 

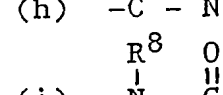
(d) 

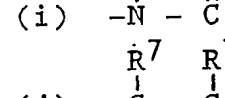
(e) 

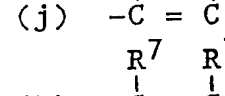
(f) 

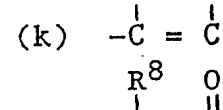
(g) 

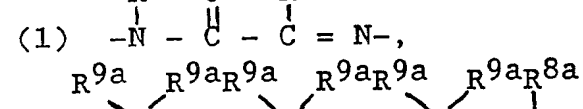
(h) 

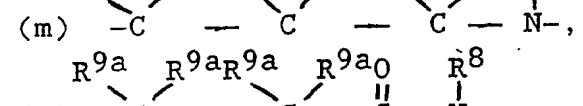
(i) 

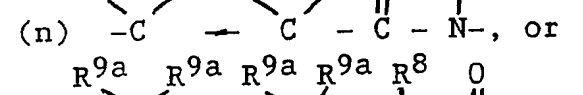
(j) 

(k) 

(l) 

(m) 

(n) 

(o) 

R^7 groups are the same or different and represent:

a) hydrogen,

b) $-C_1-C_4$-alkyl, either unsubstituted or substituted with:

i) -OH,
ii) $-CO_2R^4$,
iii) $-NH_2$,
iv) (C_1-C_4 alkyl)amino,
v) di(C_1-C_4-alkyl)amino,

c) Cl, Br, F, I,
d) $-CF_3$,
e) -OH,
f) $-N(R^4)_2$,
g) $-C_1$-C_4-alkoxy,
h) $-CO_2R^4$,
i) $-CONH_2$,
j) $-C_3$-C_7-cycloalkyl,
k) aryl,
l) heterocyclic as defined above,
m) $-CF_3$,
n) tetrazol-5-yl,
o) $-CONHSO_2R^{23}$;

R^8 groups are the same or different and represent,

a) hydrogen,
b) C_1-C_4-alkyl either unsubstituted or substituted with -OH or $-CO_2R^4$; and

R^{8a} represents

a) hydrogen,
b) C_1-C_4 alkyl, or
c) (C_1-C_4-alkyl)CO-; and

R^{9a} groups are the same or different and represent:

a) hydrogen,
b) C_1-C_4-alkyl.

Another embodiment of this invention is the group of compounds of Formula I wherein:

R^1 is:

(a) $-SO_2NHCOR^{23}$,

(b) $-SO_2NHCONR^9R^{23}$,

(c) $-SO_2NHCOOR^{23}$,

(d) $-SO_2NHOR^{23}$,

(e) $-CH_2SO_2NHCOR^{23}$, or

(f) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are independently:

a) C_1-C_4-alkyl, or

b) chloro,

c) hydrogen;

R^{3a} and R^{3b} are independently:

a) C_1-C_4-alkyl,

b) chloro, or

c) C_1-C_4-alkoxy,

d) hydrogen;

E is a single bond or -S-;

R^6 is

(a) a branched or straight chain C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which is either unsubstituted or substituted with C_1-C_4-alkylthio, C_1-C_4-alkoxy, CF_3, CF_2CF_3 or $-CF_2CH_3$;

(b) C_3-C_7-cycloalkyl;

(c) perfluoro-C_1-C_4-alkyl;

A-B-C-D- represents:

(a) $-C(R^7)=C(R^7)-C(R^7)=C(R^7)-$,

(b) $-C(R^7)=C(R^7)-C(R^7)=N-$,

(c) $-C(R^7)=C(R^7)-N=C(R^7)-$,

(d) $-N=C(R^7)-N=C(R^7)-$,

(e) $-C(R^7)=N-C(R^7)=N-$,

(f) $-N=C(R^7)-C(R^7)=N-$,

(g) $-N=N-C(R^7)=C(R^7)-$,

(h) $-C(=O)-N(R^8)-C(=O)-N(R^8)-$,

(i) $-N(R^8)-C(=O)-N(R^8)-C(=O)-$,

(j) $-C(R^7)=C(R^7)-C(=O)-N(R^8)-$,

(k) $-N(R^8)-C(=O)-C(R^7)=N-$,

(l) $-N-C(R^7)-N(R^8)-C(=O)$, or

(m) $-C(R^7)=C(R^7)-N(R^8)-C(=O)-$;

R^7 groups are the same or different and represent:

a) hydrogen,

b) $-C_1-C_4$-alkyl, either unsubstituted or substituted with -OH or $-CO_2R^4$,

c) Cl, Br, F, I,
d) -OH,
e) $-N(R^4)_2$,
f) $-C_1-C_4$-alkoxy, or
g) $-CO_2R^4$,
h) aryl,
i) heterocyclic as defined above,
j) $-CF_3$,
k) tetrazol-5-yl,

R^8 groups are the same or different and represent:
a) H,
b) C_1-C_4-alkyl either unsubstituted or substituted with -OH or $-CO_2R^4$.

In a class of this embodiment are those compounds of Formula I wherein:

R^1 is:
(a) $-SO_2NHCOR^{23}$,
(b) $-SO_2NHCONR^9R^{23}$,
(c) $-SO_2NHCOOR^{23}$,
(d) $-SO_2NHOR^{23}$,
(e) $-CH_2SO_2NHCOR^{23}$, or
(f) -1H-tetrazol-5-yl;

E is a single bond; and

A-B-C-D represents:

(a) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}}-$,

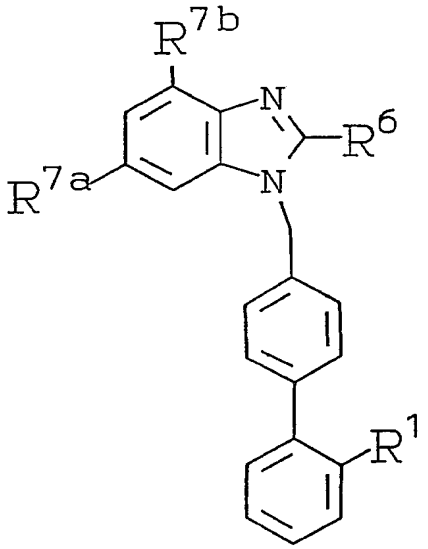
(b) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{R^7}{\underset{|}{C}} = N-$,

(c) $-\overset{R^7}{\underset{|}{C}} = N - \overset{R^7}{\underset{|}{C}} = N-$, or

(d) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{O}{\overset{\|}{C}} - \overset{R^8}{\underset{|}{N}}-$.

Exemplifying this class are the compounds shown in Tables I and II

TABLE I

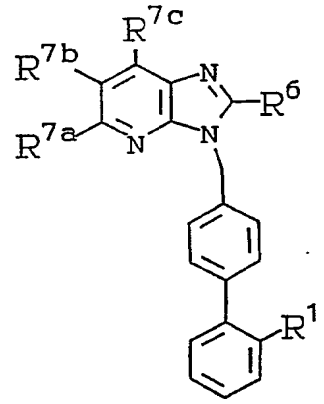


R^1	R^6	R^{7a}	R^{7b}
SO_2NHCO-Ph	ethyl	methyl	methyl
SO_2NHCO-4-pyridyl	ethyl	methyl	methyl
SO_2NHCO-propyl	ethyl	methyl	methyl
SO_2NHCO-n-heptyl	ethyl	methyl	methyl
$SO_2NHCOCH_2CH_2$-cyclopentyl	ethyl	methyl	methyl
SO_2NHCO-(3-aminophenyl)	ethyl	methyl	methyl

R^1	R^6	R^{7a}	R^{7b}
$SO_2NHCOCH_2NHBoc$	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NH_2$	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NHBoc$	ethyl	methyl	methyl
$SO_2NHCOCH_2NH_2$	ethyl	methyl	methyl
SO_2NHCO-(4-methoxyphenyl)	ethyl	methyl	methyl
SO_2NHCO-cyclopropyl	ethyl	CO_2Me	methyl
SO_2NHCO-(4-aminophenyl)	ethyl	CO_2Me	methyl
$SO_2NHCOCH_2CH_2CO$-N-morpholinyl	ethyl	methyl	methyl
SO_2NHCO-2-thienyl	ethyl	CO_2Me	methyl
$SO_2NHCO(CH_2)_5NHBoc$	ethyl	CO_2Me	methyl
$SO_2NHPO(OCH_2Ph)_2$	ethyl	methyl	methyl
$SO_2NHCOCF_2Cl$	ethyl	methyl	methyl
SO_2NHSO_2-N-methyl-N-piperidinyl	ethyl	methyl	methyl
$SO_2NHCO_2CH_2CH_3$	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_3NH_2$	ethyl	methyl	methyl
SO_2NHCO-3-aminophenyl	ethyl	CO_2Me	methyl
SO_2NHCO-4-dimethylamino	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NHBoc$	cyclopropyl	methyl	methyl
SO_2NHCO-4-tolyl	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_4CO_2Et$	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_4CO_2H$	ethyl	methyl	methyl
SO_2NHCO-phenyl	cyclopropyl	methyl	methyl
SO_2NHCO-N-morpholinyl	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5N(CH_3)_2$	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NH_2$	ethyl	methyl	methyl
SO_2NHCO-4-(N-t-butoxy-carbonylpiperidinyl)	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_2CH(NHBoc)$-$(CO_2t$-Bu)	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_6NH_2$	ethyl	methyl	methyl

R^1	R^6	R^{7a}	R^{7b}
SO_2NHCO-cyclopropyl	ethyl	CH_2OH	methyl
SO_2NHCO-2-thiazolyl	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_3NHt$-Boc	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_3NHt$-Boc	ethyl	methyl	methyl
SO_2NHCO-cyclopropyl	ethyl	$CON(CH_3)_2$	methyl

Table II



R^1	R^6	R^{7a}	R^{7b}	R^{7c}
SO_2NHCOphenyl	ethyl	methyl	bromine	methyl
tetrazol-5-yl	butyl	methyl	N(benzyl)CObutyl	H
tetrazol-5-yl	butyl	methyl	$NHCON(phenyl)_2$	H

The compounds of Formula (I) can be synthesized using the reactions and techniques described in published European Patent Applications EP 400,835 and EP 400,974 (Merck & Co.). The above mentioned applications disclose the compounds of this

invention where they are alleged to be angiotensin II receptor antagonists useful in the treatment of hypertension and ocular hypertension.

The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocycle and in the reactants being employed should be consistent with the chemical transformations being conducted. Depending upon the reactions and techniques employed, optimal yields may require changing the order of synthetic steps or use of protecting groups followed by deprotection.

The compounds useful in the novel method treatment of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkai metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic, toluenesulfonic, maleic, fumaric, camphorsulfonic.

The salts can be formed by conventional means, such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such

as water which is then removed *in vacuo* or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

Neurotensin is a peptide hormone and the assays described below have been developed to identify neurotensin antagonists and to determine their efficacy *in vitro*. The following two assays have been employed for that purpose.

RAT FOREBRAIN RECEPTOR ASSAY

Male rats are sacrificed by decapitation following ether anesthetization. Forebrains are homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The final pellet is washed twice by rehomogenization and centrifugation as before. The final pellet is resuspended at a concentration of 8 mg tissue (wet weight) per 0.750 ml of 50 µM Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4 µg/ml bacitracin, 5 µM levocabastine HCl, 1mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenyl methyl sulfonyl fluoride. Assay tubes (13 X 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [^{125}I]neurotensin 3) 20 µl test compounds 4) 750 µl tissue suspension and 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvestor with GF/B

filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 X 4 ml of ice cold 10 mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 X 75 mM polypropylene tubes for counting on as Packard Multi-Prias gamma counter.

HUMAN HT-29 CELL MEMBRANE ASSAY

HT-29 cells were routinely grown in 225 cm^2 Costar tissue culture flasks at 37°C in a humidified atmosphere of 5% CO_2/95% air in Dulbecco's modified Eagle's medium with high glucose containing 50 U/ml penicillin, 50 µg/ml streptomycin, 5% fetal bovine serum and 5% newborn calf serum. Cells were subcultured with 0.25% trypsin at a ratio of 1:6 with confluence being reached at 48 to 72 hrs. Cells from confluent flasks (approx. 1 x 10^8 cells/flask) were harvested by scraping. The cells were pelleted by centrifugation (1000 x g, 5 min), resuspended in 50 mM Tris HCl, pH 7.4, and homogenized with a polytron (setting 7 for 10 sec.). Cell membranes were washed twice by centrifugation (50,000 x g, 15 min) and rehomogenization. The resulting pellet was either frozen at -70°C for future use or run directly in the assay by resuspending at a concentration of 0.5 x 10^6 cells per 0.750 ml of assay buffer (50 mM Tris HCl, pH 7.4, containing 1 mM EDTA, 40 µg/ml bacitracin, 1 mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenylmethylsulfonyl fluoride).

Assay tubes (13 x 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [^{125}I]neurotensin 3) 20 µl test compounds 4) 750 µl cell membrane suspension an 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temperature, the samples are filtered using a Brandel M24 cell harvestor with GF/B filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml of ice cold 10 mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on as Packard Multi-Prias gamma counter. [The above assay is derived from the assay described in Kitabgi, P. et al., Molecular Pharmacology, 18, 11-19 (1980)].

NEUROTENSIN BINDING ASSAY USING HUMAN FRONTAL CORTEX

Post-mortem human brain is obtained through the National Disease Research Interchange (Philadelphia, PA). The donors were without psychiatric or neurological abnormalities. Frontal cortex is dissected free of white matter and homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The resulting pellet is washed twice by rehomogenization and centrifugation as before. The final pellet is resuspended at a concentration of 8 mg tissue (wet weight) per 0.750 ml of 50 mM Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4 µg/ml bacitracin, 1 mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenyl methyl sulfonly

fluoride. Assay tubes (13 x 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [^{125}I]neurotensin 3) 20 µl test compounds 4) 750 µl tissue suspension and 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvestor with GF/B filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml of ice cold 10mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on a Packard Multu-Prias gamma counter.

Using the methodology described above, representative compounds of the invention were evaluated and all were found to exhibit an activity of at least IC_{50}<50µM thereby demonstrating and confirming the utility of the compounds of the invention as effective neurotensin antagonists.

Typically, these combinations can be formulated into pharmaceutical compositions as discussed below.

About 1 to 100 mg. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the unit dosage unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occuring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples further illustrate the preparation of the compounds of Formula I and their incorporation into pharmaceutical compositions

and, as such, are not to be considered or construed as limiting the invention recited in the appended claims.

2-Butyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 7)

2-propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 8)

Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl-7-3H-imidazo[4,5-b]pyridine (Example 9)

2-butyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 10)

8-Butyl-1,3-dimethyl-7-(2'-(tetrazol-5-yl)biphen-4-yl) methyl-1,2,3,6-tetrahydro-2,6-dioxopurine (Example 11)

6-Chloro-8-propyl-9-(2'-tetrazol-5-yl)biphen-4-yl)-methylpurine (Example 15)

5,7-Dimethyl-2-ethyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 16)

5,7-Dimethyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 17)

2-Butyl-5,7-dimethyl-3-(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 18)

5-Amino-2-propyl-3-(2'-(tetrazol-5-yl)biphenyl-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 20)

2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 21)

2,7-dimethyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 22)

7-Methyl-2-pentyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 23)

7-methyl-2-nonyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 24)

2-Isopropyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl) methyl-3H-imidazo[4,5-b]pyridine (Example 25)

7-Methyl-2-(3-methyl)propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 26)

2-Cyclopropyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 27)

2-Methoxymethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 28)

8-Propyl-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine (Example 29)

8-Butyl-6-chloro-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine (Example 30)

8-Butyl-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine (Example 31)

2-Chloro-6-methyl-8-propyl-9-(2'-(tetrazol-5-yl)-biphen-4-yl)methylpurine (Example 32)

2-Dimethylamino-6-methyl-8-propyl-9-(2'-(tetrazol-5-yl)-biphen-4-yl)methylpurine (Example 33)

6-Methyl-2-methylamino-8-propyl-9-(2'-(tetrazol-5-yl)-biphen-4-yl)methylpurine (Example 34)

6-Methyl-2-(morpholin-4-yl)-8-propyl-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine (Example 35)

7-Methyl-3-(2'-(N-(phenylsulfonyl)carboxamido-biphen-4-yl)methyl-2-propyl-3H-imidazo[4,5-b]pyridine (Example 37)

3-(2'-(N-(4-Chloro)phenylsulfonylcarboxamido)biphen-4-yl)methyl-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine (Example 38)

2-Cyclopropyl-5,7-dimethyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 40)

7-Methyl-2-propyl-3-(2'trifluoromethylsulfonamido-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 41)

7-Methyl-2-propyl-3-(2'-trifluoromethylsulfonamido-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 42, Step 5)

5,7-Dimethyl-2-ethyl-3-(2'-trifluoromethylsulfonamido-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 43, Step 3)

3-(2'-(N-Acetyl)sulfonamidomethylbiphen-4-yl)methyl-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine (Example 43, Step 9)

5-Bromo-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 44)

5-Chloro-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 45)

5-Cyano-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 46)

5-Carboxy-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 47)

5-(Ethoxycarbonyl)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine (Example 48)

2-Ethyl-5-(methoxycarbonyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine (Example 49)

5-(Benzyloxycarbonyl)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine (Example 50)

2-Ethyl-5-(iso-propyloxycarbonyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine (Example 51)

5-(n-Butyloxycarbonyl)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine (Example 52)

5-Carboxamido-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 53)

2-Ethyl-7-methyl-5-(morpholin-4-yl)carbonoyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 54)

2-Ethyl-7-methyl-5-(isopropyl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 55)

5-Ethyl-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 56)

2-Ethyl-5-(n-hexyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 57)

2-Ethyl-7-methyl-5-phenyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 58)

2-Ethyl-7-methyl-5-(tetrazol-5-yl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 59)

5-Acetyl-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 60)

2-Ethyl-5-((RS)-1-hydroxy)ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 61)

2-Ethyl-5-(hydroxymethyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 62)

2-Ethyl-5-(2-hydroxyprop-2-yl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 63)

2-Ethyl-5-(3-hydroxypent-3-yl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 64)

5-Amino-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 65)

5-Amino-2-ethyl-7-(trifluoromethyl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 66)

2-Ethyl-5-(methylamino)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 67)

5-(Dimethylamino)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 68)

5-(Methylamino)-2-propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 69)

5-(Dimethylamino)-2-propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 70)

2-Ethyl-5-(hexylamino)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 71)

5-(2-Aminoethyl)amino-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 72)

5-(Carboxymethyl)amino-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 73)

2-Ethyl-7-methyl-5-(4-morpholino)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 74)

2-Ethyl-7-methyl-5-(methylthio)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 75)

2-Ethyl-5-hydroxy-7-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 76)

5-Ethoxy-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 77)

5-(Acetamidoethyl)amino-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 78)

2-Ethyl-5-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 79)

5-Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 80)

6-Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 81)

6-Bromo-7-methyl-2-propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 82)

7-Ethyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 83)

7-Isopropyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 84)

7-Ethyl-2-ethyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 85)

6-Hydroxymethyl-7-methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 86)

2-Propyl-7-(p-tolyl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 87)

2-Propyl-7-methyl-6-(p-tolyl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 88)

5-Chloro-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 89)

6-Amino-5,7-dimethyl-2-propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 90)

7-Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine-4-oxide (Example 91)

5,7-Dimethyl-6-hydroxy-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 92)

5,7-Dimethyl-2-(3,3,3-trifluoroprop-2-yl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 93)

2-(3-Butyn-1-yl)-5,7-dimethyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 94)

5,7-Dimethyl-2-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 95)

7-Chloro-2-ethyl-5-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 96)

2-Ethyl-5-methyl-7-(4-morpholino)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 97)

2-Ethyl-5-methyl-7-(methylamino)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 98)

7-(Dimethylamino)-2-ethyl-5-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 99)

2-Ethyl-5-methyl-7-(methylthio)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 100)

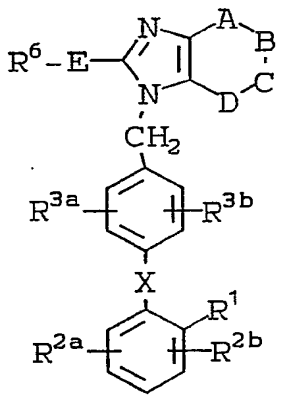
5,7-Dimethyl-2-ethyl-3-(4'-chloro-2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 101)

5,7-Dimethyl-2-ethyl-3-(4'-fluoro-2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 102)

5-(Acetoxymethyl)-2-ethyl-7-methyl-3-(2'-tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 103)

WHAT IS CLAIMED IS:

1. A method of treating gastrointestinal disorders or central nervous system disorders which comprises administering to a patient in need of such treatment a therapeutically effective amount of a neurotensin antagonist of structural formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is:

(a) $-NHSO_2R^{23}$,
(b) $-NHSO_2NHCOR^{23}$,
(c) $-NHCONHSO_2R^{23}$,
(d) $-SO_2NHR^{23}$,
(e) $-SO_2NHCOR^{23}$,
(f) $-SO_2NHCONR^9R^{23}$,
(g) $-SO_2NHCOOR^{23}$,
(h) $-SO_2NHOR^{23}$,

(i) $-CH_2SO_2NHCOR^{23}$,
(j) $-CH_2SO_2NHCONHR^{23}$,
(k) $-CO_2H$, or
(l) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are independently H, Cl, Br, I, F, $-NO_2$, $-NH_2$, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, $-SO_2NHR^9$, CF_3, C_1-C_4-alkyl, or C_1-C_4-alkoxy;

R^{3a} is
(a) H,
(b) Cl, Br, I, F,
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy,
(e) C_1-C_6-alkoxyalkyl;

R^{3b} is
(a) H,
(b) Cl, Br, I, F,
(c) NO_2,
(d) C_1-C_6-alkyl,
(e) C_1-C_6-acyloxy,
(f) C_1-C_6-cycloalkyl
(g) C_1-C_6-alkoxy,
(h) $-NHSO_2R^4$,
(i) hydroxy C_1-C_4-alkyl,
(j) aryl C_1-C_4-alkyl,
(k) C_1-C_4-alkylthio,
(l) C_1-C_4-alkyl sulfinyl,
(m) C_1-C_4-alkyl sulfonyl,
(n) NH_2,

(o) C_1-C_4-alkylamino,
(p) C_1-C_4-dialkylamino,
(q) fluoro C_1-C_4-alkyl,
(r) $-SO_2-NHR^9$,
(s) aryl, or wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of Cl, Br, I, F, C_1-C_4-alkyl, C_1-C_4-alkoxy, NO_2, CF_3, C_1-C_4-alkylthio, OH, NH_2, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$, CO_2H, and CO_2-C_1-C_4-alkyl;
(t) furyl;

R^4 is H, C_1-C_6 alkyl, aryl or $-CH_2$-aryl;

R^{4a} is C_1-C_6-alkyl, aryl or $-CH_2$-aryl;

R^5 is H, $-\underset{\displaystyle R^4}{\underset{|}{CH}}-O-\overset{\displaystyle O}{\overset{\|}{C}}-R^{4a}$;

E is a single bond, $-NR^{13}(CH_2)_s-$,$-S(O)_x-(CH_2)_s-$ where x is 0 to 2 and s is 0 to 5, $-CH(OH)-$, $-O-$, $-CO-$;

R^6 is
(a) aryl unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Cl, Br, I, F, $-O-C_1$-C_4-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1$-C_4-alkyl, $-OH$, $-NH_2$, C_3-C_7-cycloalkyl, C_3-C_{10}-alkenyl;

(b) C_1-C_9-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which can be unsubstituted or substituted with a substituent selected from the group consisting of aryl, C_3-C_7-cycloalkyl, Cl, Br, I, F, -OH, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-CF_2CF_3$, $-N(C_1$-C_4-alkyl$)_2$, $-NH-SO_2R^4$, $-COOR^4$, $-CF_3$, $-CF_2CH_3$, $-SO_2NHR^9$; or

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered cyclic ring which can contain one or two members selected from the group consisting of N, O, S, and wherein the substituents are members selected from the group consisting of -OH, -SH, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, Cl, Br, I, F, or NO_2,

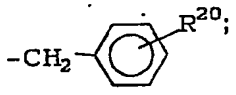
(d) perfluoro-C_1-C_4-alkyl,

(e) C_3-C_7-cycloalkyl optionally mono- or disubstituted with C_1-C_4-alkyl or $-CF_3$;

R^9 is H, C_1-C_5-alkyl, aryl or $-CH_2$-aryl;

R^{10} is H, C_1-C_4-alkyl;

R^{11} is H, C_1-C_6-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, or



R^{12} is $-CN$, $-NO_2$ or $-CO_2R^4$;

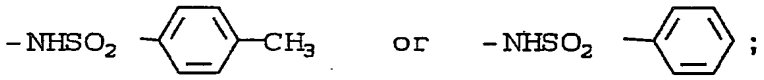
R^{13} is H, $-CO(C_1-C_4\text{-alkyl})$, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{15} is H, C_1-C_6-alkyl;

R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,



;

R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;

R^{20} is H, $-NO_2$, $-NH_2$, $-OH$ or $-OCH_3$;

R^{22} is

(a) phenyl, unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of: Cl, Br, I, or F, $-O-C_1-C_4$-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1-C_4$-alkyl, $-OH$, $-NH_2$, $-COOR^4$, C_3-C_7-cycloalkyl, and C_3-C_{10}-alkenyl;

(b) C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, C_3-C_7-cycloalkyl, Cl, Br, I, F, -OH, -O-C_1-C_4-alkyl, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, $-NH-SO_2R^4$, $-COOR^4$, $-SO_2NHR^9$, and -S-C_1-C_4-alkyl;

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered ring comprising one or two heteroatoms selected from the group consisting of N, O, and S, and wherein the substituents are members selected from the group consisting of: -OH, -SH, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, $-COOR^4$, Cl, Br, I, F, and NO_2; or

(d) C_3-C_7-cycloalkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: C_1-C_4-alkyl, -O-C_1-C_4-alkyl, -S-C_1-C_4-alkyl, -OH, $-COOR^4$, C_1-C_4-perfluoroalkyl, Cl, Br, F, and I, or

(e) (C_1-C_4)-perfluoroalkyl;

R^{23} is

(a) aryl,

(b) heteroaryl,

(c) C_3-C_4-cycloalkyl,

(d) C_1-C_8-alkyl which can be unsubstituted or substituted with one or two substituents selected from the group consisting of:

aryl, heteroaryl, wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five- or six-membered aromatic ring which can optionally contain 1 to 3 heteroatoms selected from the group consisting of O, N or S and wherein the substituents are members selected from the group consisting of: -OH, -SH, $-C_1-C_4$-alkyl, $-O(C_1-C_4$-alkyl), $-S(C_1-C_4$-alkyl), $-C_3-C_8$-cycloalkyl, $-CF_3$, Cl, Br, F, I, $-NO_2$, $-CO_2H$, $-CO_2-C_1-C_4$-alkyl, $-CONR^4R^{22}$, $-OCONR^4R^{22}$, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-NHCOR^{4a}$, NR^4COOR^9 $-N(C_1-C_4$-alkyl$)_2$, $-NR^4COR^{22}$, $-NR^4SO_2R^{22}$, $-SO_2NR^4R^{22}$, $-PO_3H$, $-PO(OH)(C_1-C_4$-alkyl), $-PO(OH)$(aryl), or $-PO(OH)(O-C_1-C_4$-alkyl), or

(e) perfluoro-C_1-C_4-alkyl;

X is absent or is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,

(e) $-\underset{\displaystyle R^{13}}{\overset{|}{N}}-$,

(f) $-CO\underset{\displaystyle R^{15}}{\overset{|}{N}}-$,

(g) $-\underset{\displaystyle R^{15}}{\overset{|}{N}}CO-$,

(h) $-OCH_2-$,

(i) $-CH_2O-$

(j) $-SCH_2-$,

(k) $-CH_2S-$,

(l) $-NHC(R^9)(R^{10})$,

(m) $-NR^9SO_2-$,

(n) $-SO_2NR^9-$,

(o) $-C(R^9)(R^{10})NH-$,

(p) $-CH=CH-$,

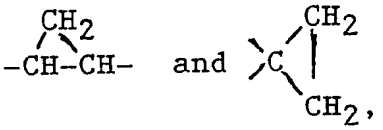
(q) $-CF=CF-$,

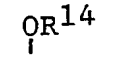
(r) $-CH=CF-$,

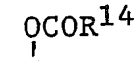
(s) $-CF=CH-$,

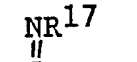
(t) $-CH_2CH_2-$,

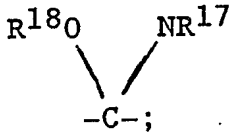
(u) $-CF_2CF_2-$,

(v)  and ,

(w)  ,

(x)  ,

(y)  , or

(z)  ;

Z is O, NR^{13} or S;

-A-B-C-D- represents the constituent atoms of a 6-member carbocycle or a 6-member saturated or unsaturated heterocyclic ring with the imidazole to which they are attached containing 1 to 3 nitrogen atoms and includes the following:

(a) $-C(R^7)=C(R^7)-C(R^7)=C(R^7)-$,

(b) $-C(R^7)=C(R^7)-C(R^7)=N-$,

(c) $-N=C(R^7)-C(R^7)=C(R^7)-$,

(d) $-C(R^7)=C(R^7)-N=C(R^7)-$,

(e) $-C(R^7)=N-C(R^7)=C(R^7)-$,

(f) $-C(R^7)=C(R^7)-N=N-$,

(g) $-N=N-C(R^7)=C(R^7)-$,

(h) $-C(R^7)=N-N=C(R^7)-$,

(i) $-N=C(R^7)-C(R^7)=N-$,

(j) $-N=C(R^7)-N=C(R^7)-$,

(k) $-C(R^7)=N-C(R^7)=N-$,

(l) $-N=N-N=\overset{R^7}{\overset{|}{C}}-$,

(m) $-\overset{R^7}{\overset{|}{C}}=N-N=N-$,

(n) $-N=N-\overset{R^7}{\overset{|}{C}}=N-$,

(o) $-N=\overset{R^7}{\overset{|}{C}}-N=N-$,

(p) $-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-$,

(q) $-\overset{R^8}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-$,

(r) $-\overset{R^7}{\overset{|}{C}}=\overset{R^7}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-$,

(s) $-\overset{R^8}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-\overset{R^7}{\overset{|}{C}}=N-$,

(t) $-N=\overset{R^7}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-$,

(u) $-\overset{R^7}{\overset{|}{C}}=\overset{R^7}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-$,

(v) $-\overset{R^7}{\overset{|}{C}}=\overset{R^7}{\overset{|}{C}}-\overset{R^8}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-$,

(w) $-\overset{R^8}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-\overset{R^7}{\overset{|}{C}}=\overset{R^7}{\overset{|}{C}}-$,

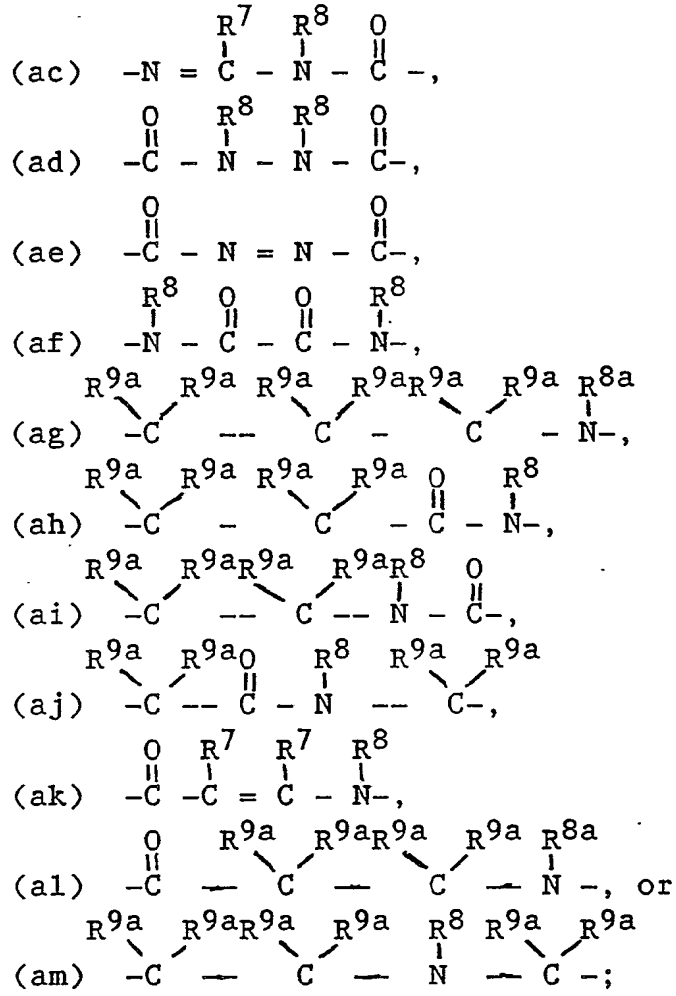
(x) $-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-\overset{R^7}{\overset{|}{C}}=\overset{R^7}{\overset{|}{C}}-$,

(y) $-\overset{R^8}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-N=N-$,

(z) $-N=N-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-$,

(aa) $-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-N=N-$,

(ab) $-\overset{O}{\overset{\|}{C}}-\overset{R^8}{\overset{|}{N}}-\overset{R^7}{\overset{|}{C}}=N-$,



R^7 groups can be the same or different and represent:

a) hydrogen,

b) C_1-C_6 straight or Br,anched chain alkyl, or C_2-C_6 alkenyl, or alkynyl each of which is unsubstituted or substituted with:

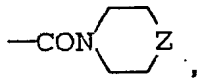
i) -OH

ii) C_1-C_4-alkoxy,

iii) $-CO_2R^4$,

iv) $-OCOR^4$,

v)



vi) $-CON(R^4)_2$

vii) $-N(R^4)-CR^4$

viii) $-N(R^4)_2$,

ix) aryl as defined above,

x) heterocyclic as defined in (p) below,

xi) $-S(O)_xR^{23}$,

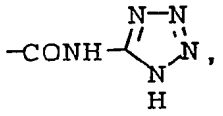
xii) tetrazol-5-yl,

xiii) $-CONHSO_2R^{23}$,

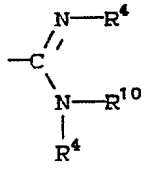
xiv) $-SO_2NH$-heteroaryl,

xv) $-SO_2NHCOR^{23}$,

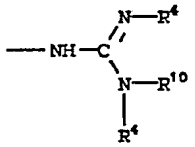
xvi)



xvii)



xviii)



xix) $-PO(OR^4)_2$,

xx) $-PO(OR^4)R^9$,

c) Cl, Br, I, F,

d) perfluoro-C_1-C_4-alkyl,

e) -OH,

f) $-NH_2$,

g) $-\underset{\underset{R^4}{|}}{N}-R^{23}$,

h) $-\underset{\underset{R^4}{|}}{N}-COR^{23}$,

i) $-OR^{23}$,

j) $-CO_2R^4$,

k) $-CON(R^4)_2$,

l) -NH-C_3-C_7-cycloalkyl,

m) C_3-C_7-cycloalkyl,

n) aryl as defined above, or

o) heterocyclic which is a five- or six-membered saturated or unsaturated ring containing up to three heteroatoms selected from the group consisting of O, N or S wherein S may in the form of sulfoxide or sulfone and which may be optionally substituted with one or two substituents which are members selected

from the group consisting of halo(Cl, Br, F, I), C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-$S(O)_x$- where x is as defined above, CF_3, NO_2, OH, CO_2H, CO_2-C_1-C_4-alkyl, or $-N(R^4)_2$;

p) -CN,

q) $(CH_2)_nN$- wherein n is 4 to 6,

r) $-SO_2N(R^4)_2$;

s) tetrazol-5-yl,

t) $-CONHSO_2R^{23}$,

u) $-PO(OR^4)_2$,

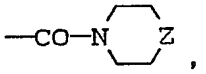
v) $-NHSO_2CF_3$,

w) $-SO_2NH$-heteroaryl,

x) $-SO_2NHCOR^{23}$,

y) $-S(O)_x-R^{23}$,

z)



aa) $-PO(OR^4)R^9$,

bb) $-NHSO_2R^{23}$,

cc) $-NHSO_2NHR^{23}$,

dd) $-NHSO_2NHCOR^{23}$,

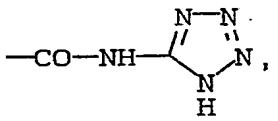
ee) $-NHCONHSO_2R^{23}$,

ff) $-N(R^4)CO_2R^{23}$,

gg) $-\underset{R^4}{N}-\underset{R^4}{CON}-R^{23}$,

hh) -CO-aryl,

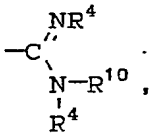
ii)



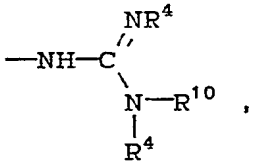
jj) $-CO-C_1-C_4$-alkyl,

kk) $-SO_2NH-CN$,

ll)



mm)



R^8 groups can be the same or different and represent:

a) hydrogen,

b) C_1-C_6-alkyl or alkenyl either unsubstituted or substituted with hydroxy, C_1-C_4-alkoxy, $-N(R^4)_2$, $-CO_2R^4$, or C_3-C_5-cycloalkyl;

c) C_3-C_5-cycloalkyl,

R^{8a} is R^8 or C_1-C_4-acyl;

R^{9a} groups can be the same or different and represent:

a) hydrogen,

b) C_1-C_6-alkyl either unsubstituted or substituted with

i) hydroxy,

ii) $-CO_2R^4$,

iii) $-CONHR^4$, or

iv) $-CON(R^4)_2$.

2. The method of Claim 1, wherein:

R^1 is:

(a) $-NHSO_2R^{23}$,

(b) $-NHSO_2NHCOR^{23}$,

(c) $-NHCONHSO_2R^{23}$,

(d) $-SO_2NHR^{23}$,

(e) $-SO_2NHCOR^{23}$,

(f) $-SO_2NHCONR^9R^{23}$,

(g) $-SO_2NHCOOR^{23}$,

(h) $-SO_2NHOR^{23}$,

(i) $-CH_2SO_2NHCOR^{23}$,

(j) $-CH_2SO_2NHCONHR^{23}$, or

(k) -1H-tetrazol-5-yl;

X is a single bond;

R^{2a} and R^{2b} are independently:

(a) C_1-C_4-alkyl,

(b) halogen,

(c) hydrogen;

R^{3a} and R^{3b} are independently:

(a) C_1-C_6-alkyl,

(b) halogen, or

(c) C_1-C_6-alkoxy,

(d) hydrogen;

R^4 is H, or C_1-C_4-alkyl;

E is a single bond or -S-;

R^6 is a Br,anched or straight chain C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl or C_2-C_6- alkynyl each of which is either unsubstituted or substituted with C_1-C_4- alkylthio, C_1-C_4-alkoxy, CF_3, CF_2CF_3 or $-CF_2CH_3$;

A-B-C-D- represents:

(a) $-\overset{R^7}{C} = \overset{R^7}{C} - \overset{R^7}{C} = \overset{R^7}{C}-$,

(b) $-\overset{R^7}{C} = \overset{R^7}{C} - \overset{R^7}{C} = N-$,

(c) $-\overset{R^7}{C} = \overset{R^7}{C} - N = \overset{R^7}{C}-$,

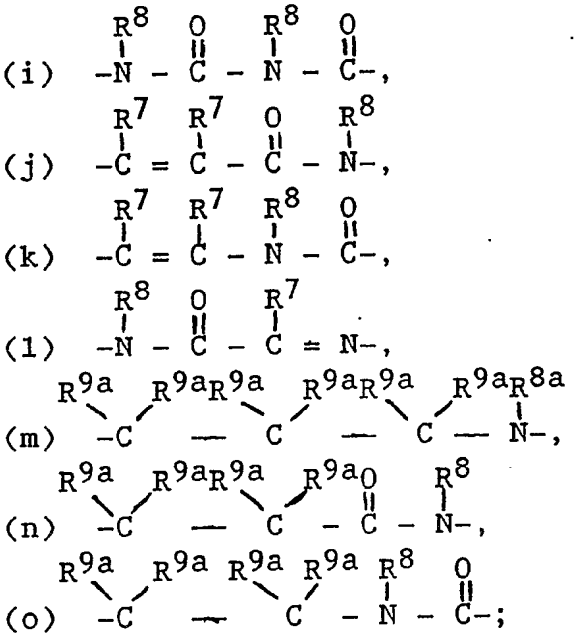
(d) $-N = \overset{R^7}{C} - N = \overset{R^7}{C} -$,

(e) $-\overset{R^7}{C} = N - \overset{R^7}{C} = N-$,

(f) $-N = \overset{R^7}{C} - \overset{R^7}{C} = N-$,

(g) $-\overset{R^7}{C} = \overset{R^7}{C} - N = N -$,

(h) $-\overset{O}{\overset{\|}{C}} - \overset{R^8}{N} - \overset{O}{\overset{\|}{C}} - \overset{R^8}{N}-$,



R^7 groups are the same or different and represent:

(a) hydrogen,

(b) $-C_1-C_4$-alkyl, either unsubstituted or substituted with:

i) $-OH$,

ii) $-CO_2R^4$,

iii) $-NH_2$,

iv) (C_1-C_4 alkyl)amino,

v) di(C_1-C_4-alkyl)amino,

(c) Cl, Br, I, F,

(d) $-CF_3$,

(e) $-OH$,

(f) $-N(R^4)_2$,

(g) $-C_1-C_4$-alkoxy,

(h) $-CO_2R^4$,

(i) $-CONH_2$,

(j) $-C_3-C_7$-cycloalkyl,
(k) aryl,
(l) heterocyclic as defined above,
(m) $-CF_3$,
(n) tetrazol-5-yl,
(o) $-CONHSO_2R^{23}$,;

R^8 groups are the same or different and represent,
(a) hydrogen,
(b) C_1-C_4-alkyl either unsubstituted or substituted with -OH or $-CO_2R^4$; and

R^{8a} represents
(a) hydrogen,
(b) C_1-C_4 alkyl, or
(c) $(C_1-C_4$-alkyl$)CO-$; and

R^{9a} groups are the same or different and represent:
(a) hydrogen,
(b) C_1-C_4-alkyl.

3. The method of Claim 1 wherein:

R^1 is:
(a) $-SO_2NHCOR^{23}$,
(b) $-SO_2NHCONR^9R^{23}$,
(c) $-SO_2NHCOOR^{23}$,
(d) $-SO_2NHOR^{23}$,
(e) $-CH_2SO_2NHCOR^{23}$, or
(f) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are independently:

(a) C_1-C_4-alkyl,

(b) chloro, or

(c) hydrogen;

R^{3a} and R^{3b} are independently:

(a) C_1-C_4-alkyl,

(b) chloro, or

(c) C_1-C_4-alkoxy, or

(d) hydrogen;

E is a single bond or -S-;

R^6 is

(a) a Br,anched or straight chain C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which is either unsubstituted or substituted with C_1-C_4-alkylthio, C_1-C_4-alkoxy, CF_3, CF_2CF_3 or $-CF_2CH_3$;

(b) C_3-C_7-cycloalkyl;

(c) perfluoro-C_1-C_4-alkyl;

A-B-C-D- represents:

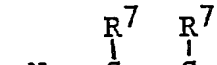
(a) $-\overset{R^7}{C} = \overset{R^7}{C} - \overset{R^7}{C} = \overset{R^7}{C}-$,

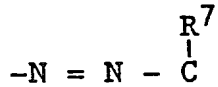
(b) $-\overset{R^7}{C} = \overset{R^7}{C} - \overset{R^7}{C} = N-$,

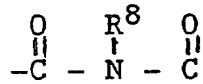
(c) $-\overset{R^7}{C} = \overset{R^7}{C} - N = \overset{R^7}{C}-$,

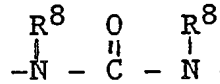
(d) $-N = \overset{R^7}{C} - N = \overset{R^7}{C} -$,

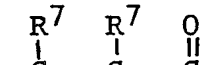
(e) $-\overset{R^7}{C} = N - \overset{R^7}{C} = N-$,

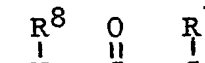
(f) 

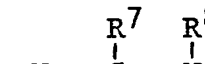
(g) 

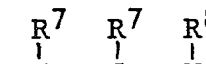
(h) 

(i) 

(j) 

(k) 

(l)  or

(m)  ;

R^7 groups are the same or different and represent:

(a) hydrogen,

(b) $-C_1-C_4$-alkyl, either unsubstituted or substituted with -OH or $-CO_2R^4$,

(c) Cl, Br, I, or F,

(d) -OH,

(e) $-N(R^4)_2$,

(f) $-C_1-C_4$-alkoxy, or

(g) $-CO_2R^4$,

(h) aryl,

(i) heterocyclic as defined above,

(j) $-CF_3$,

(k) tetrazol-5-yl,

R^8 groups are the same or different and represent:

(a) H,

(b) C_1-C_4-alkyl either unsubstituted or substituted with -OH or $-CO_2R^4$.

4. The compound of Claim 3 wherein:

R^1 is:

(a) $-SO_2NHCOR^{23}$,

(b) $-SO_2NHCONR^9R^{23}$,

(c) $-SO_2NHCOOR^{23}$,

(d) $-SO_2NHOR^{23}$,

(e) $-CH_2SO_2NHCOR^{23}$, or

(f) -1H-tetrazol-5-yl;

E is a single bond;

A-B-C-D represents:

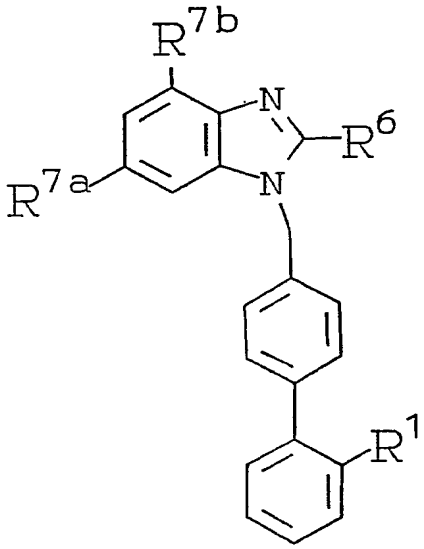
(a) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}}-$,

(b) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{R^7}{\underset{|}{C}} = N-$,

(c) $-\overset{R^7}{\underset{|}{C}} = N - \overset{R^7}{\underset{|}{C}} = N-$ or

(d) $-\overset{R^7}{\underset{|}{C}} = \overset{R^7}{\underset{|}{C}} - \overset{O}{\underset{\|}{C}} - \overset{R^8}{\underset{|}{N}}-$.

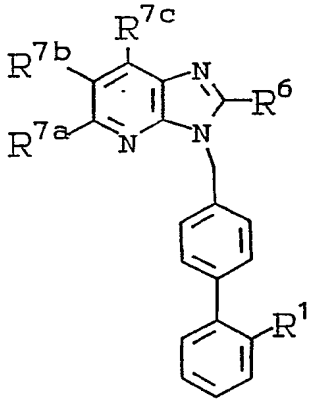
5. The method of Claim 4 wherein the compound is selected from the group consisting of:



R^1	R^6	R^{7a}	R^{7b}
SO_2NHCO-Ph	ethyl	methyl	methyl
SO_2NHCO-4-pyridyl	ethyl	methyl	methyl
SO_2NHCO-propyl	ethyl	methyl	methyl
SO_2NHCO-n-heptyl	ethyl	methyl	methyl
$SO_2NHCOCH_2CH_2$-cyclopentyl	ethyl	methyl	methyl
SO_2NHCO-(3-aminophenyl)	ethyl	methyl	methyl
$SO_2NHCOCH_2NHBoc$	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NH_2$	ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NHBoc$	ethyl	methyl	methyl
$SO_2NHCOCH_2NH_2$	ethyl	methyl	methyl
SO_2NHCO-(4-methoxyphenyl)	ethyl	methyl	methyl

SO_2NHCO-cyclopropyl		ethyl	CO_2Me	methyl
SO_2NHCO-(4-aminophenyl)		ethyl	CO_2Me	methyl
$SO_2NHCOCH_2CH_2CO$-N-morpholinyl		ethyl	methyl	methyl
SO_2NHCO-2-thienyl		ethyl	CO_2Me	methyl
$SO_2NHCO(CH_2)_5NHBoc$		ethyl	CO_2Me	methyl
$SO_2NHPO(obenzyl)_2$		ethyl	methyl	methyl
$SO_2NHCOCF_2Cl$		ethyl	methyl	methyl
SO_2NHSO_2-N-methyl-N-piperidinyl		ethyl	methyl	methyl
$SO_2NHCO_2CH_2CH_3$		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_3NH_2$		ethyl	methyl	methyl
SO_2NHCO-3-aminophenyl		ethyl	CO_2Me	methyl
SO_2NHCO-4-dimethylamino		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NHBoc$	cyclopropyl		methyl	methyl
SO_2NHCO-4-tolyl		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_4CO_2Et$		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_4CO_2H$		ethyl	methyl	methyl
SO_2NHCO-phenyl	cyclopropyl		methyl	methyl
SO_2NHCO-N-morpholinyl		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5N(CH_3)_2$		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_5NH_2$		ethyl	methyl	methyl
SO_2NHCO-4-(N-t-butoxycarbonyl-piperidinyl)		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_2CH(NHBoc)(CO_2t\text{-}Bu)$		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_6NH_2$		ethyl	methyl	methyl
SO_2NHCO-cyclopropyl		ethyl	CH_2OH	methyl
SO_2NHCO-2-thiazolyl		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_3NHt\text{-}Boc$		ethyl	methyl	methyl
$SO_2NHCO(CH_2)_3NHt\text{-}Boc$		ethyl	methyl	methyl
SO_2NHCO-cyclopropyl		ethyl	$CON(CH_3)_2$	methyl.

6. The method of Claim 4 wherein the compound is selected from the group consisting of:



R^1	R^6	R^{7a}	R^{7b}	R^{7c}
SO_2NHCOphenyl	ethyl	methyl	bromine	methyl
tetrazol-5-yl	butyl	methyl	N(benzyl)CObutyl	H
tetrazol-5-yl	butyl	methyl	$NHCON(phenyl)_2$	H.

7. The method of Claim 1 wherein the gastrointestinal disorder is selected from the group consisting of gastroesophagal reflux disorder (GERD), irritable bowel syndrome, diarrhea, cholic, ulcer, GI tumors, dyspepsia, pancreatitis, esophagitis and gastroparesis.

8. A pharmaceutical composition useful in the treatment of gastrointestinal disorders which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as recited in Claim 1.

9. The method of Claim 1 wherein the central nervous disorder is selected from the group consisting of psychoses, depression, cognitive dysfunction, and anxiety, tardive dyskinesia, drug dependency, panic attack and mania.

10. A pharmaceutical composition useful in the treatment of cental nervous system disorders which comprises a pharmaceutically acceptable carrier and a pharmaceutically acceptable amount of a compound as recited in Claim 1.

11 The use of a compound as defined in any of claims 1-6 in the preparation of a medicine for the treatment of a condition as defined in any of claims 1, 7 or 10.